II.—THE LEUCOCYTES IN MALARIAL FEVER: A METHOD OF DIAGNOSING MALARIA LONG AFTER IT IS APPARENTLY CURED

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Prefatory Note.

This research was carried on in the Tropical Ward of the Royal Southern Hospital, Liverpool, under the direction of Major R. Ross, C.B., F.R.S. The new facts obtained are the result of numerous daily observations extending over periods of several weeks. The laboriousness of the work was much diminished by the use of a new blood-counting pipette devised by the author. The method is based on 'The Thick Film Process' [Ross, 1903]. The funds for the research have been supplied by the Advisory Committee of the Colonial Office.

I. THE LEUCOCYTES DURING ACTIVE MALARIA *

During active malaria the number of leucocytes is, as a general rule, less than normal, but the numbers vary with the rise and fall of temperature. When the fever is in full force, that is during the rigor and high temperature, then there is a coincident diminution of the total leucocytes in the peripheral blood. In this diminution the polymorphonuclear as well as mononuclear leucocytes take part. If we take 7,000 per c.mm. as the normal leucocyte count, and the normal percentage of polymorphonuclears and total mononuclears as 65 per cent. and 35 per cent. respectively, then normally the polymorphonuclear leucocytes should number

* In this article I refer to charts in Paper I ('The Production, Life and Death of Crescents,' etc.).

about 4,550 per c.mm. of blood and the total mononuclears about 2,450 per c.mm. of blood. During a malarial temperature, however, the polymorphs are frequently less than 2,000 per c.mm., and the total mononuclears are also frequntly below this number. In some cases the total leucocyte count during the pyrexia may be as low as 2,000 per c.mm. of blood. In other exceptional cases, however, I have seen a marked leucocytosis during a high malarial temperature. This occurred in two cases of comatose malaria. It is rare, however, and I think it may be taken as a general rule that there is a leucopenia in malaria when the temperature is above normal. In other words, during the actual sporulation of the malarial parasites there is a diminution of the total leucocytes in the peripheral blood. This rule holds good with the benign tertian, malignant tertian and quartan parasites. Some observers have described a transient polymorphonuclear leucocytosis lasting only for one half-hour just at the commencement of a rigor. I have so far been unable to confirm this. After the sporulation is over and the temperature has fallen, it will be found that the total number of leucocytes has increased even up to normal numbers or more, so that in the intervals after the temperatures the leucopenia disappears, and may occasionally even have its place taken by a leucocytosis; but on the advent of the next sporulation and temperature, the numbers again fall. Thus with the rise and fall of temperature in malaria we have a corresponding fall and rise in the total number of leucocytes. The diminution of total leucocytes corresponds exactly with the rise of temperature, and the rise of total leucocytes corresponds exactly with the fall of temperature. See Charts N.B. Case 9, J.W. Case 30, and Billet's Chart [1908]. We may therefore enunciate a general law as follows:—

Law I. *During active malaria the number of total leucocytes in the peripheral blood is below normal, and varies more or less inversely with the temperature.*

When one analyses the different varieties of leucocytes, it is found that the mononuclears, and especially the large mononuclears, play most part in the variation enunciated in this law. In this research, however, I have considered only the total polymorphonuclear leucocytes and the total mononuclears. So many

transitional forms of leucocytes occur between the recognised varieties that a considerable personal factor comes into play, and in dealing with all varieties one increases the complications very much. Thus if we consider only the two chief classes of leucocytes with regard to Law I, it may be stated that the total polymorphonuclear leucocytes vary only slightly with the temperature in active malaria, but that the total mononuclears vary very much and inversely with the temperature. In other words, the sporulations of the malarial parasite cause a greater disturbance or reaction among the mononuclear than among the polymorphonuclear leucocytes. When the spores of the malarial parasite escape free into the blood plasma there occurs a mononuclear leucopenia, followed later by a mononuclear excess. This is exactly the reverse of what happens when a bacterial culture is injected intravenously into an animal. Here the result is a polymorphonuclear leucopenia followed by a polymorphonuclear excess (F. W. Andrewes [1910]).

In malarial fever the mononuclear leucocytes, especially the large variety, are undoubtedly the soldiers for defence. They ingest the spores of the malarial parasite in large numbers. Some hours after a malarial paroxysm or sporulation the large mononuclear leucocytes are found in great numbers filled with vacuoles and pigment, due to the active ingestion of parasites. If it were not for this phagocytic power of this class of leucocyte, it is likely that the parasites would become more and more numerous after each paroxysm, and the patient would soon succumb. When the mononuclears gain the upper hand and exist in large numbers the fever disappears spontaneously for a time. This is noticeable in Chart J.W., Case 30, where the patient had no relapse, though no quinine was given for fourteen days. This natural mononuclear defence is greatly assisted by the administration of quinine. After a dose of twenty to thirty grains of quinine the fever frequently disappears quite suddenly. Corresponding to this sudden disappearance of fever there is a fall in the number of parasites and a large increase of mononuclear leucocytes. This phenomenon occurs in many of the cases studied. The mononuclear increase continues so long as the fever does not return. It would therefore appear that an increase in the total mononuclear leucocytes is

coincident with periods of resistance or immunity to the disease. Previous to a relapse the number of leucocytes invariably falls (*vide* Charts W.M. [*P. vivax*], Case 17, R.B., and Case 20, F.B.). From these facts we have therefore the basis of another law, though this law is really only a different expression of Law I.

Law II. *In malarial fever the curve representing the percentage of total mononuclear leucocytes is the exact inverse of the temperature curve*: in other words, if one makes frequent daily differential counts of the leucocytes in malarial fever, on charting the varying percentage of total mononuclears, one finds the curve obtained is the exact inverse of the temperature curve. See Charts M.G. (*P. vivax*), and G.J., Case 34 (*P. falciparum*).

When the temperature in malaria is rising, the total mononuclear percentage is falling, and *vice versa* the fall of temperature is exactly simultaneous with a rise in the total mononuclear percentage. At the height of his fever, J.W., Case 30, had only 39·4 per cent. of total mononuclear leucocytes. He received twenty grains of quinine. Next day he had no fever, and the total mononuclears were 80 per cent. This rise is chiefly due to the large mononucleated variety. In Case 8, P.D., after the first dose of quinine the fever soon ceased, and the large mononuclears rose from 19 per cent. to 65 per cent. in one day. I have observed occasionally a total mononuclear percentage as high as 90 per cent. I have not met with any exceptions so far to Law II. It would seem that a high mononuclear percentage is incompatible with a true malarial temperature.

From the above law it would seem reasonable, as a therapeutic measure in malaria, to attempt to increase the leucocytes, especially those of the mononuclear type. Recently it was discovered that an injection of an extract of leucocytes, causes a marked increase of leucocytes in the peripheral blood in a few hours (Ross and Thomson [1911], Alexander [1911]). A case of malaria was treated with this substance (Lambert [1909]), and it was found that the injection prevented the rigors from occurring. It is highly probable that this phenomenon was due to the increase in leucocytes following these injections. The extracts made and used by Alexander consist chiefly of the polymorph variety of leucocytes, and produce, after injection, chiefly a polymorph excess. We would

expect to obtain better results from injections of a mononuclear leucocytic extract, but unfortunately so far, it is very difficult to obtain such a substance. Before leaving the question of therapeutics, I would refer to Charts J.M. (leprosy), D.T. (normal person), and J.L., Case 53 (*P. vivax*). From these it will be seen that injections of pilocarpine in doses of one-tenth of a grain produce quite a definite excess of the mononucleated variety of leucocytes in the peripheral blood, (*vide* researches by Waldstein [1895]). In Chart J.L., Case 53, it will be noticed that during the injections of pilocarpine in the above doses the mononuclear percentage as well as the total leucocytes maintained a high level, and that the fever disappeared without other treatment. As this, however, frequently occurs naturally without any treatment when patients are kept in bed in comfortable circumstances, one cannot come to definite conclusions until further work has been done in this line.

II. THE BEHAVIOUR OF THE LEUCOCYTES IN QUIESCENT OR LATENT MALARIA, AND IN MALARIA APPARENTLY CURED BY QUININE OR OTHER TREATMENT

Laws I and II deal with the leucocytes where the malarial parasites are numerous and easily found and where true paroxysms of fever occur. When, however, we observe further the leucocytes during the latency or apparent convalescence and cure of the disease, we find some remarkable differences. During active malaria, as already stated, the leucocytes, on the whole below normal numbers, show periodic variations in number, due chiefly to fluctuations of the mononuclear variety. In convalescent or apparently cured malaria, however, where the temperature remains more or less below normal, we have a similar periodic variation; but this time the variations are due chiefly to fluctuations in the polymorphonuclear variety, and the leucocytes on the average are greatly in excess of the normal number (*vide* Chart C.H., Case 38). This change from a fluctuation in the number of mononuclears to a greater fluctuation in the number of polymorphonuclears seems to take place invariably. A certain time elapses after the active malaria before this new leucocytic phenomenon begins. If the malaria has been severe, or if the patient is much debilitated, it is

not noticeable for perhaps ten days or longer, while in other cases, usually less severe, it may occur in a few days to about a week. It also occurs whether the patient has recovered as a result of quinine treatment or not, and is therefore not due to quinine treatment (*vide* Chart W.M. (*P. vivax*)). Again the fluctuation is very markedly periodic, occurring daily or on alternate days or irregularly. Thus if the fever was quotidian, tertian or irregular there is evidence to show that these fluctuations in total leucocytes (chiefly due to polymorphs) are also quotidian, tertian or irregular. This would seem to indicate that there is some malarial periodic virus lingering in the system in spite of vigorous quinine treatment of thirty grains daily, and where no fever parasites can be detected on microscopic examination of the blood. If the total mononuclear percentage is charted as before, it is found that the percentage is low when the total leucocytes are high, and the curve representing the total mononuclears does not vary nearly so much as the curve of the total polymorphonuclears (*vide* Chart 38, C.H.). Law II, however, still holds good, the mononuclear percentage being as a rule lowest when the temperature is highest, although the temperature may at no time rise above normal. It would thus appear that this transient periodic increase of leucocytes, chiefly due to polymorphonuclears, is due possibly to minute numbers of asexual parasites sporulating at regular intervals. If this is so, then it would appear that the sudden liberation into the blood of large doses of the malarial virus causes a leucopenia, while small doses cause a leucocytosis. This periodic leucocytosis occurs at the time of the day at which the patient previously had a rigor and fever. Another possible explanation is that it is due to the periodic outburst of sexual forms or gametes into the peripheral circulation. (See accompanying paper on 'Crescents.') Against this explanation, it is found to occur when no gametes have been produced, and also long after they have disappeared owing to quinine treatment. In Case C.H. 38, it almost seems as if the daily outburst of crescents caused a daily polymorphonuclear increase. It would seem, however, that the polymorphonuclear leucocytes seldom or never ingest crescents. In cases with very numerous crescents and absence of asexual parasites many pigmented mononuclear leucocytes are found, but only very occasionally does one find a

pigmented polymorphonuclear leucocyte. It would therefore appear that the mononuclear leucocytes ingest not only the asexual parasites, but also the sexual forms or gametes. Whether the gametes can be ingested alive or only after their death is a matter for speculation. It is interesting to note that the change from a mononuclear into a polymorphonuclear swing often takes place about the time that crescents first appear in the peripheral circulation, that is a week to ten days after the last paroxysm of fever. In the preceding article on 'Crescents,' pages 65 and 66, I have pointed out that an increase of leucocytes seems to be coincident with increase of immunity and consequent crescent production, and that in quiescent malaria the leucocytes are in greater numbers than normal. These periods of quiescence often continue for ten or more days, though no quinine be given, and it would almost seem that the relapses tend to occur when the polymorphonuclear leucocytes begin to play more part in the increase of leucocytes. This, however, is only speculation. Beyond these suggestions, I am unfortunately unable to give any explanation of this most interesting phenomenon, which I will enunciate as Law III.

Law III. *In convalescent or apparently cured malaria, transient periodic leucocytoses occur in the peripheral blood, and these leucocyte fluctuations arise chiefly from a polynuclear variation.*

In these periodic fluctuations the leucocytes often reach numbers as great as 40,000 to 50,000 per c.mm. of blood, and the mononuclear percentage may rarely fall as low as 20 per cent. of the total leucocytes. On one occasion I observed a leucocytosis of 125,000 per c.mm. Two hours later the number had fallen to 22,000 per c.mm., and eight hours later to 6,000 per c.mm. (Chart T.H. (*P. falc.*)).

III. A METHOD OF DIAGNOSING MALARIA NOT ONLY DURING THE ACTIVE STAGE BUT ALSO IN LATENT CASES, AND IN CASES APPARENTLY CURED BY CONTINUED QUININE TREATMENT

This new method of diagnosis depends on the constancy of Laws II and III. As already stated, there is a periodic fluctuation in the percentage of total mononuclear leucocytes in malaria. In active malaria this is due mainly to a variation in the number of

mononuclear leucocytes. This periodic fluctuating mononuclear percentage still continues in latent malaria and in cases thoroughly treated with quinine, but in these latter it is due mainly to a variation in the number of polymorphonuclear leucocytes. To apply this diagnostic test one must take frequent smears of the suspected person's blood; one smear every four to six hours is sufficient. These should be taken during a period of two to three days. Make differential counts estimating the total mononuclear percentage in each smear and plot the curve representing these percentages. If there is a more or less periodic variation in the percentage amounting to over 20 per cent., then the patient has, or has had, malarial fever. In active malaria the total mononuclear percentage usually varies somewhere between 20 per cent. and 80 per cent., the periodic swing having usually an amplitude over 20 per cent. and often as high as 40 per cent. and more. In latent and apparently cured malaria the mononuclear swing occurs at a lower level somewhere between 20 per cent. and 60 per cent. The amplitude as before is usually about 20 per cent. or over.

If the swing is irregular, then it denotes that the patient has, or has had, malarial fever of an irregular type. If the swing is distinctly quotidian or tertian, it denotes that the patient has, or had, quotidian or tertian paroxysms of fever. On examining the blood of a normal person in this way, I find that the swing of the total mononuclear percentage does not amount as a rule to more than 10 per cent., if one counts from 150 to 200 leucocytes. This 10 per cent. swing is quite irregular, and is due mainly to the error arising from the estimation of an insufficient number of leucocytes. Slight changes do, of course, take place in normal persons after exercise, meals, etc., but Chart D.T. (normal), shows clearly that these natural variations are much smaller than the marked oscillations which take place in malaria cases (*vide* Chart D.O., Case 52 (*P. vivax*), and others). Again in certain septic diseases one may have a swing in the total mononuclear percentage, but in such cases the percentage falls to a very low limit, as low as 8 per cent. to 10 per cent., and will seldom rise as high as 30 per cent., whereas in malaria the highest point of the mononuclear percentage will seldom be lower than about 45 per cent. to 50 per cent. Thus I am led to believe that a large periodic variation in the total mononuclear percentage amounting to 20 per cent., and

where the upper limit reaches over 45 per cent., is pathognomonic of malaria, and is furthermore so delicate a test that the presence of the disease or its dregs can be detected long after continued quinine administration. Moreover, by careful estimation of the percentage in this way one can also state whether the previous active fever was quotidian, tertian, or irregular in nature. It is also of great value to estimate several times daily the total leucocyte count; because, as already stated above, remarkable periodic variations in number take place, especially in quiescent or latent cases. Most of the cases show a quotidian rise of leucocytes (*vide* Charts C.H., Case 38, T.H. (*P. falc.*), etc.). The height of the leucocyte rise corresponds exactly with the lowest point of the total mononuclear percentage. This shows that this rise of leucocytes is not a digestion leucocytosis. The increase in the number of leucocytes after a meal is principally a lymphocyte increase, also the variation in number is too great to be accounted for by the natural increase after a meal. In normal persons the leucocytes seldom reach 15,000 per c.mm. after a meal. When they reach numbers over 15,000 per c.mm. it denotes some pathological condition (Beattie and Dickson [1908]). In malaria the height of the periodic rise is often as great as 30,000 per c.mm. of blood, and more rarely reaches a number as high as 40,000 to 50,000 per c.mm. Chart D.T. (normal person) shows that the natural daily variation seldom reaches 14,000 to 15,000 per c.mm. of blood.

One naturally wonders how long this abnormal leucocytic phenomenon continues after the last active attack of malarial fever. I am unable so far to answer this question, but can give some remarkable instances which show that it may continue for months, and possibly even for years.

(*a*) Case 38, C.H., shows the phenomenon with unabated force after three weeks' continuous administration of quinine 30 grains daily. Case D.O., 52, shows the same after one month of continuous treatment with quinine twenty grains daily and methylene blue twelve grains daily.

(*b*) Case J.M. (leprosy) showed the same phenomenon. This was noticed while examining the blood to see if there was any leucocyte change taking place which might be characteristic of leprosy. To my surprise the mononuclear percentage curve indicated a previous quotidian malaria. On enquiring into the

past history of this case, it was found that he had suffered from malaria four years previously. He had had no recurrence of fever since then, but stated that he remembered having a slight shivering attack five months previous to this blood examination. So far as I am aware, no one has ever described a mononuclear leucocyte excess as a characteristic of leprosy, so that one is led to the conclusion that the high mononuclear percentage with large variation was due to an infection of malaria long since apparently cured.

In the above method of diagnosis it is important to remember the already well-known fact that there is an excess of large mononuclear leucocytes in malaria. Stephens and Christophers [1908] consider a value of this variety of leucocyte above 15 per cent. as diagnostic of malaria, and there is no doubt but that these large mononuclears play most part in the total mononuclear fluctuation occurring in active malaria. They also occur in numbers above normal in apparently cured cases of malaria. Thus a diagnosis of malaria might be made from one single differential leucocyte count where the total mononuclear percentage is high, say above 50 per cent., and especially where the large mononucleated variety is in excess. Normally the large mononuclears vary from 1 per cent. to 3 per cent. of the total leucocytes (Beattie and Dickson [1909]).

The two following cases show that malaria may be diagnosed from one single differential count even months after an apparent cure:—

(*a*) Case I, W.M. (mixed infection), left hospital in March, 1910, after a thorough course of quinine and methylene blue treatment. On his discharge no parasites could be detected in his blood. He continued to take quinine in doses of five to ten grains daily until July, 1910, when he returned to hospital to report himself. During this time he had not left England. Examination of his blood revealed no parasites, but showed a total mononuclear percentage of 67 per cent. His blood was therefore still abnormal more than five months after his last attack of fever. The patient was at this time quite well.

(*b*) Case A.L.B. was treated in hospital during June and July, 1910, for malignant tertian malaria followed by blackwater fever. He returned to hospital six months later in February, 1911, to

report himself. He stated that he had been quite well for several months. His blood nevertheless showed that the total mononuclear leucocytes amounted to 62 per cent. No parasites could be detected.

Though malaria may therefore be diagnosed, or at least suspected long after its apparent cure, from one differential count, yet one count is not sufficient as a rule in these cases. The blood might happen to be taken at the lowest limit of the mononuclear swing, and might reveal a total mononuclear percentage of, say, only 20 per cent. Thus one estimation only might give a negative result, whereas several differential counts taken six hourly for two to three days would give a positive result. I think sufficient has been said to show that malaria, or at least its dregs, remain in the system for a long time after an apparent cure. It would almost seem certain that the parasites remain in the host for very long periods in spite of vigorous quinine treatment, and that they continue to develop and sporulate, giving rise to the periodic leucocyte variations described above. The case of P. T. Manson is well known, in which a relapse occurred nine months after the original infection followed by three months of quinine treatment, and where re-infection was impossible.

Before concluding, I should state that the leucocytic phenomena in blackwater fever show the malarial origin of that disease. In blackwater fever, as in malaria, the mononuclear percentage would seem also to vary inversely with the temperature.

SUMMARY

(1) During active malaria the number of leucocytes in the peripheral blood is decreased. During quiescent malaria, and in cases apparently cured by treatment, the leucocytes in the peripheral blood are much increased.

(2) During the rigor and temperature in malaria, the mononuclear leucocyte percentage (more especially that of the large mononucleated variety) is low. With the fall of temperature, however, the mononuclear percentage rises very high, sometimes even to 90 per cent. of the total leucocytes. This fluctuation in the percentage of total mononuclear leucocytes occurs also long after

continuous quinine treatment, and is observed for months and even years (?) after the last attack of fever.

(3) In these apparently cured cases of malaria, the mononuclear percentage is lowest at the time of the day at which the rigor and fever occurred during the previous active malaria; and, moreover, at this time there also occurs a very marked leucocytosis, which continues only for a few hours. The leucocytes often reach numbers as great as 30,000 to 50,000 per c.mm. of blood. On one occasion they were as numerous as 125,000 per c.mm. Two hours later they had fallen to 22,000 per c.mm., and in eight more hours there were only 6,000 per c.mm. This case showed a regular daily periodic variation in the number of leucocytes, averaging from about 6,000 per c.mm. to 50,000 per c.mm. The height of the rise always occurred about noon. This was the time at which the rigor and fever, which was quotidian, was wont to occur previously. This post-malarial leucocyte phenomenon occurred always without exception in the forty cases examined, and would therefore seem to be an infallible sign of previous malaria, as, so far, it has not been observed in any other disease.

(4) It would appear that large numbers of malarial parasites on sporulating cause a leucopenia, while a very small number on sporulating cause a leucocytosis.

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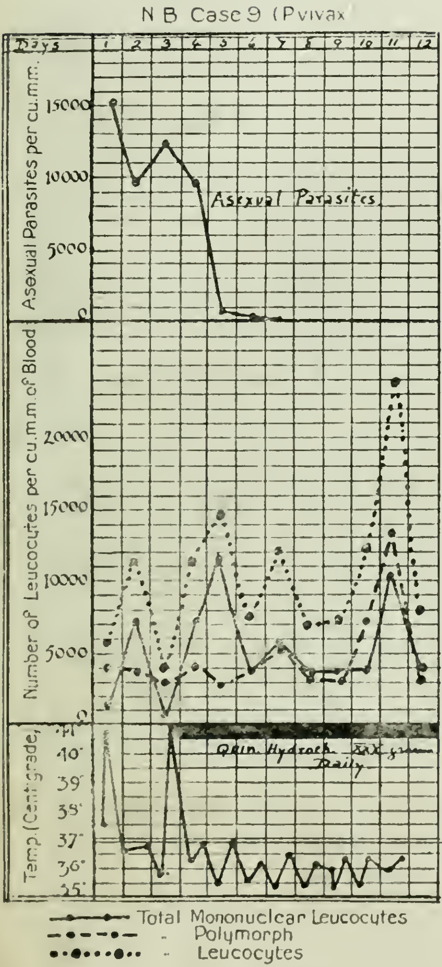
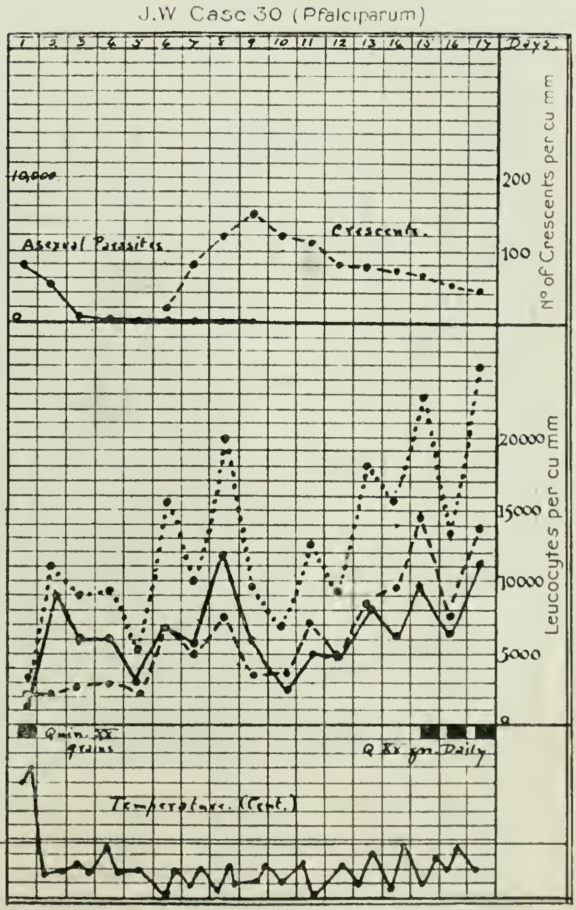

N B Case 9 (P vivax)
Days
Asexual Parasites per cu.m.m.
Asexual Parasites
Number of Leucocytes per cu.m.m. of Blood
Temp. (Centigrade)
Quin. Hydroch. XXX grs. Daily
Total Mononuclear Leucocytes
Polymorph
Leucocytes


J.W Case 30 (P falciparum)
Days
No of Crescents per cu mm
Asexual Parasites
Crescents
Leucocytes per cu mm
Quin. XX grains
Q XX gr. Daily
Temperature (Cent.)

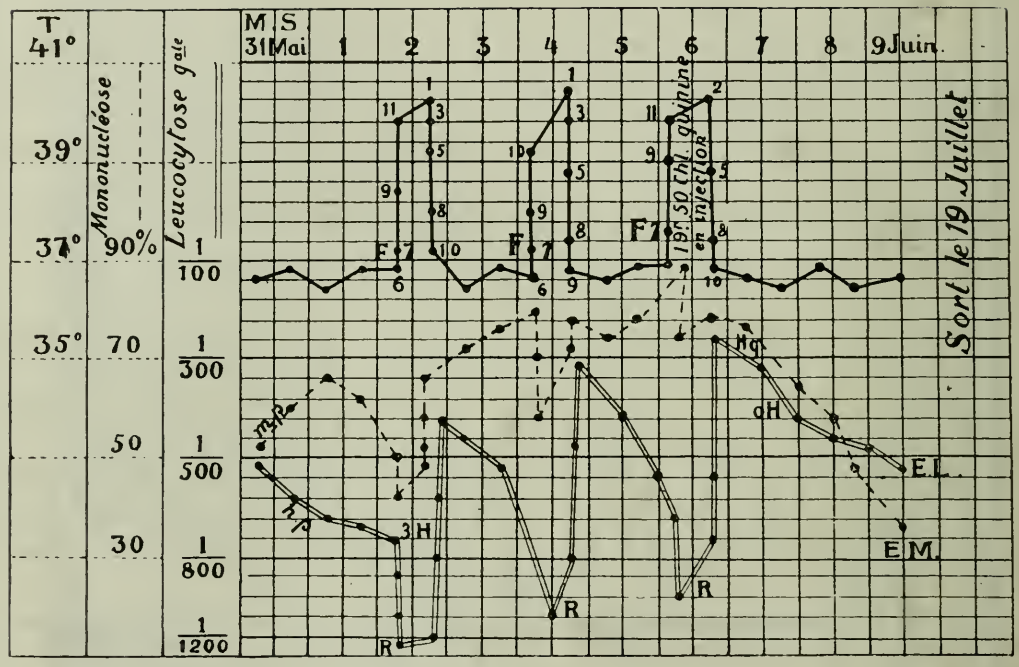
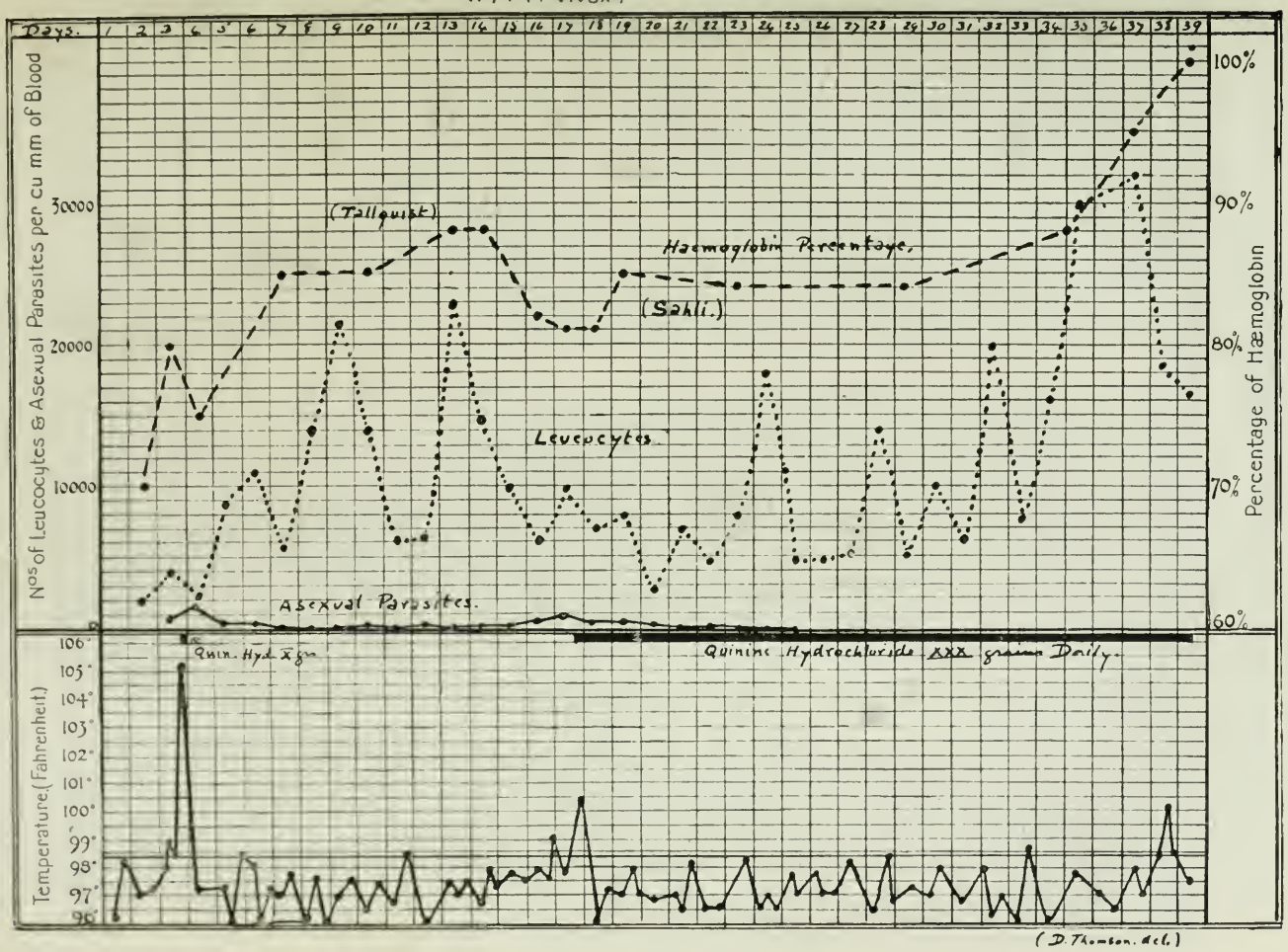
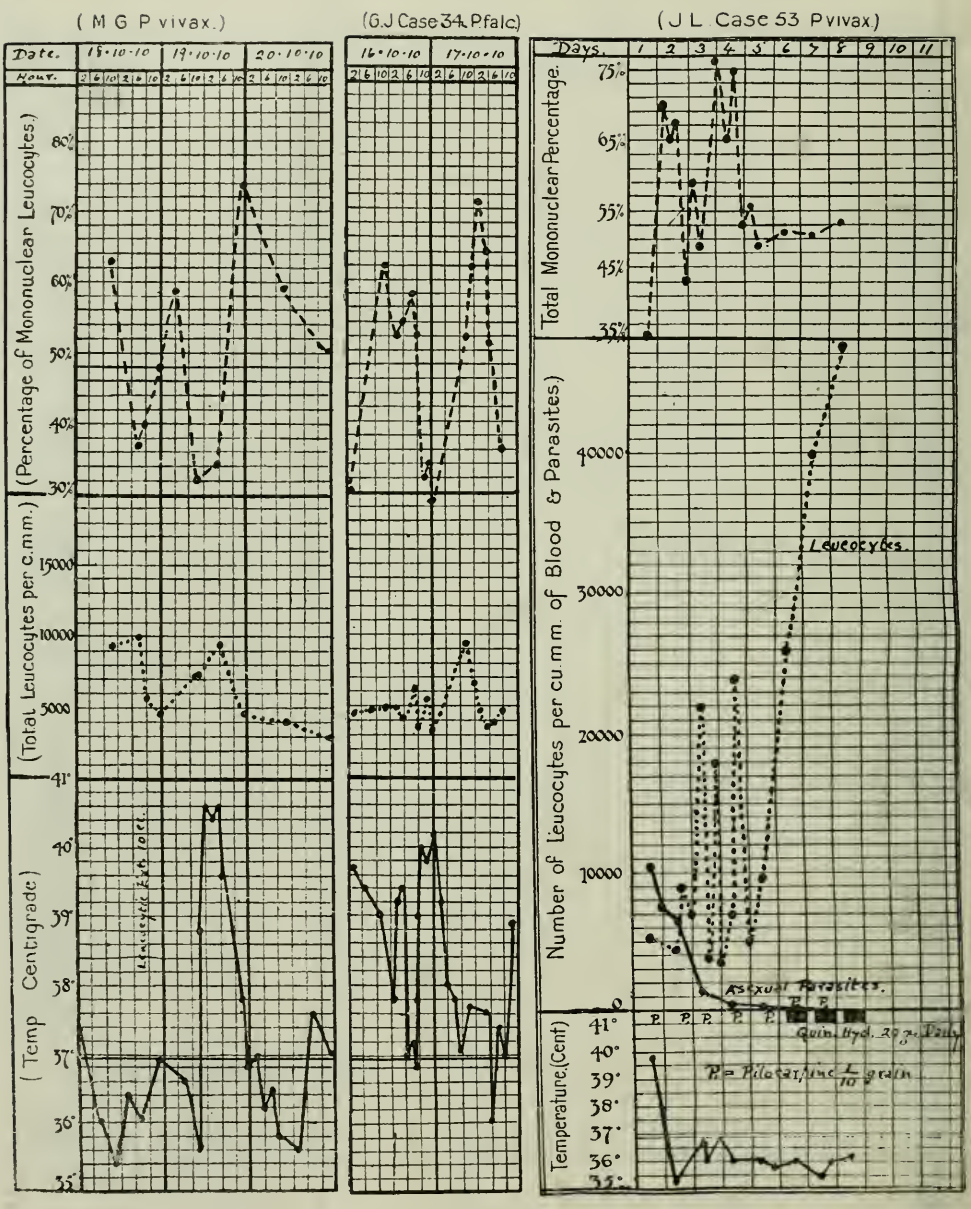


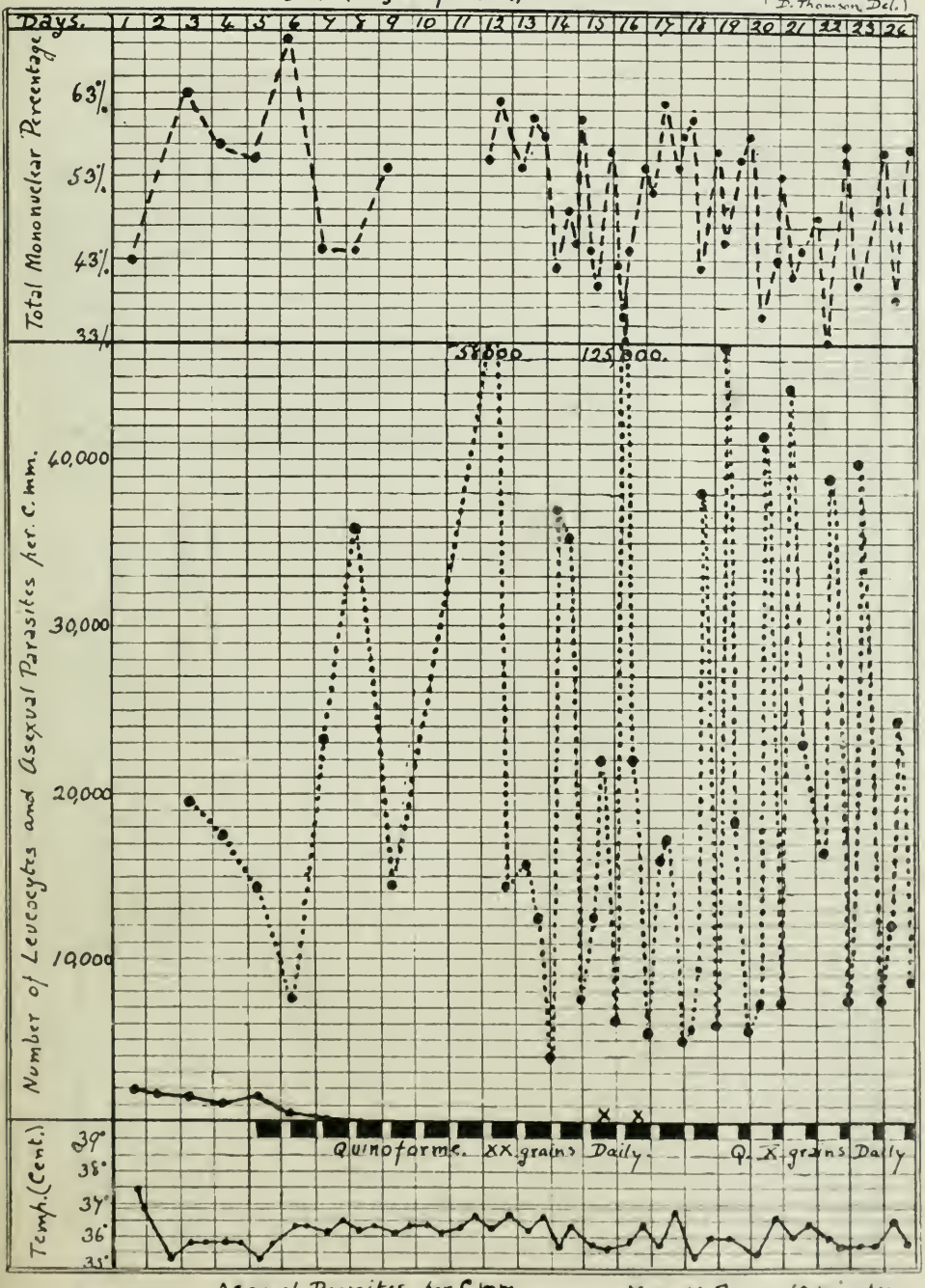
Chart shewing the changes in the total Leucocytes (and in the percentage of mononuclears large and small) in a case of simple tertian fever. The double line curve = that of total Leucocytes. (*After* Billet)


W M (P vivax)
Days.
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39
Nos of Leucocytes & Asexual Parasites per cu mm of Blood
30000
20000
10000
(Tallquist)
Haemoglobin Percentage.
(Sahli.)
Leucocytes.
Asexual Parasites.
Percentage of Hæmoglobin
100%
90%
80%
70%
60%
Temperature (Fahrenheit)
106°
105°
104°
103°
102°
101°
100°
99°
98°
97°
96°
Quin. Hyd. Xgm
Quinine Hydrochloride XXX grains Daily.
(D. Thomson. del.)


(M G P vivax.)
(G.J Case 34 Pfalc)
(J L Case 53 P vivax)
Date.
Hour.
15·10·10
16·10·10
17·10·10
19·10·10
20·10·10
Days.
(Percentage of Mononuclear Leucocytes.)
Total Mononuclear Percentage.
(Total Leucocytes per c.m.m.)
Number of Leucocytes per cu m m. of Blood & Parasites)
Leucocytes.
Asexual Parasites.
Quin. Hyd. 20 gr. Daily.
P = Pilocarpine 1/10 grain
(Temp Centigrade)
Temperature (Cent)

T. H. (P. falciparum.)

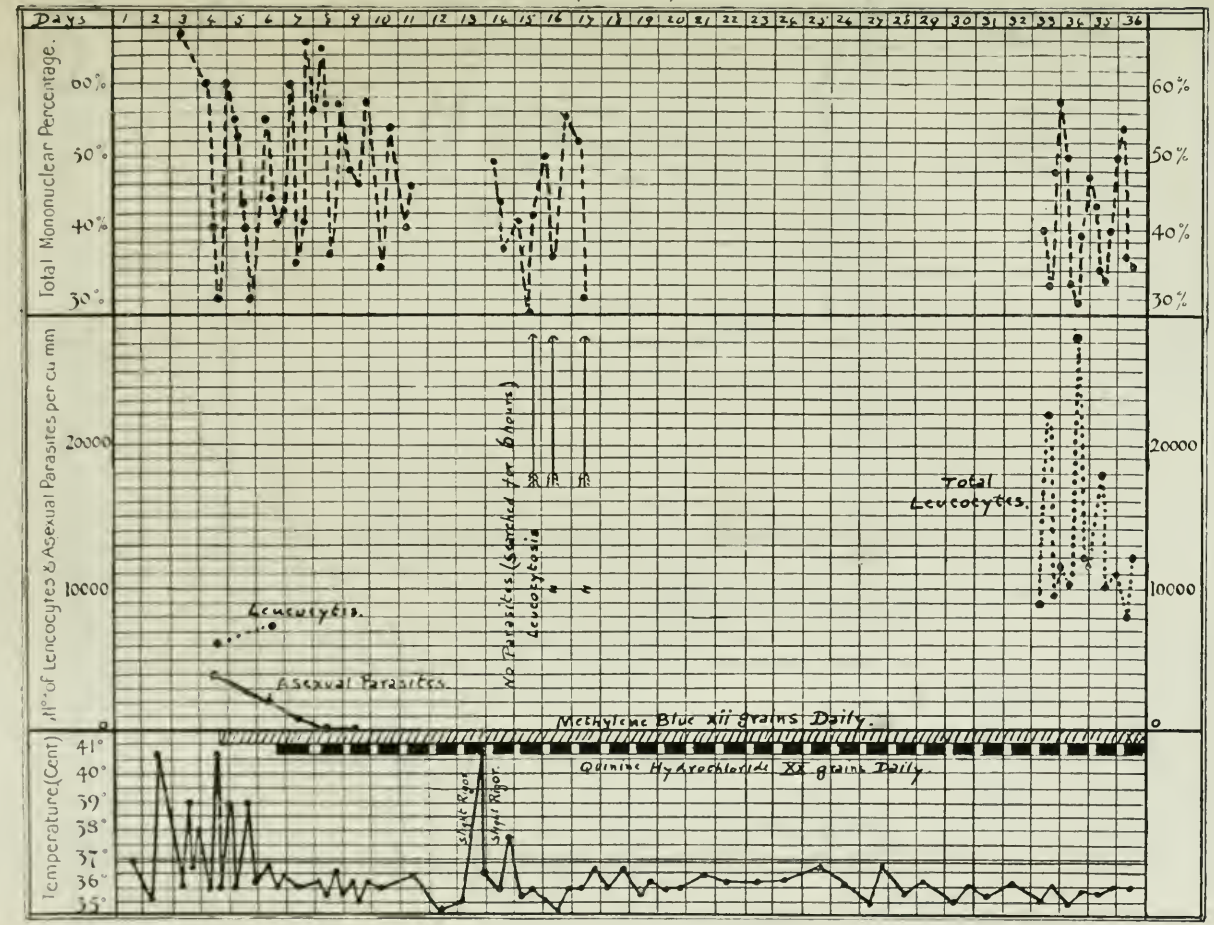
(D. Thomson, Del.)



D.T. (Normal)

Number of Leucocytes per cu mm of Blood
30000
20000
10000
0
Total Mononuclear Percentage.
50%
40%
30%
Days
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 1. 2. 1 2 3 4 5 6 7 8 9 10
Leucocytic Extract 15 mm empfehl.
Spleen Extract 1.0.
x Pilocarpin 1/6 grain.
x Pilocarpin 1/4 grain.

D O Case 52. (P vivax.)



J.M. Leprosy. (Old Malaria Case.)